REMARKS

Claims 44 and 47-54 are under consideration and claims 34-43 and 45-46 have been cancelled.

Claim 54 is supported by Table 2 and the key at page 12. Note that 5-HT is a mediator or marker (see Claim 50), [3H]-5-hydroxytryptamine release.

Claim Rejections - 35 U.S.C. § 112

In paragraph 4 at page 2 of the Office Action, the Examiner rejects claims 45 and 47 under 35 U.S.C. § 112, first paragraph, as lacking a written description in the specification.

A. The Examiner alleges there is no support in the specification for the method of claim 45 wherein the cell-line is "sensitized prior to said exposing."

Claim 45 has been cancelled, making this part of the rejection moot.

B. The Examiner alleges that there is no support in the specification for reciting that the pre-selected substance results in at least 3-45% mediator release, because Figure 4 only refers to release of radiolabeled 5HT in response to one specific pre-selected substance.

Claim 47 has been amended to recite only that the cell-line is a secretor variant, thereby overcoming this part of the rejection.

In paragraph 5 of the Office Action, the Examiner rejects claim 45 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Since claim 45 has been cancelled, this rejection is moot.

In paragraph 6 of the Office Action, the Examiner rejects claims 44-53 under 35 U.S.C. § 112, first paragraph, as not being enabled.

The Examiner refers to *Benyon et al.* as evidence that the presently claimed method cannot work. Specifically, the Examiner states that *Benyon et al.* teach that mast cells release histamine, a cell mediator, in response to both allergens and nonallergens. Therefore, the Examiner concludes that release of cell mediators in response to a pre-selected substance could not be indicative of the allergenicity of the substance.

Contrary to the Examiner's position, *Benyon et al.* in fact support the viability of the invention. The method of the present invention is looking for substances which cause non-immunological mediator release. Therefore *Benyon et al.'s* results support the present invention, although *Benyon et al.* did not recognize the significance of their observation in relation to potential allergenicity, since the molecular mechanisms leading to the development of allergic responses were less well defined at the time their observation was made. *Benyon et al.* deduced that the mediator release was due to an incidental factor, such as the closeness of some mast cell populations to nerve endings. In fact the skilled artisan at the time would not, on reading *Benyon et al.,* have appreciated that the release observed was an indication of potential allergenicity.

One of ordinary skill in the art on reading *Benyon et al.* and being equipped with the knowledge and understanding which has been built up since 1989 by progress in this field, but particularly in view of the knowledge built up from the inventors on work leading to the present invention, would appreciate that *Benyon et al.* had in fact observed non IgE mediated release, which he has termed non-immunological, and which is indicative of potential allergenicity in individuals. The present invention therefore shows that substances have been observed in the past, for example by *Benyon et al.,* to induce release of then-unrecognized mediators, which have since been classified as mediators, and the substances classified as allergens.

In fact, it is for exactly this reason that a substance could today be observed to cause cell release of an unrecognized substance or a substance whose physiological effect is unknown, and, significantly whose potential as allergen is unknown, but the substance could, in a number of years, after the effect of the substance released has been researched, be observed to be a potential allergen. The present invention provides a method for screening substances to identify potential allergens. In the method, and this was initially the surprising observation, the mediators released by most potential allergens in the absence of IgE sensitization are the same as those released as a result of an IgE-mediated antigenic stimulus. In fact there are now several hundred such mediators including isoforms that have been identified, and there could well be more mediators which have not yet been identified.

It is now known that people can get stress induced asthma attacks, allergies, etc., which are not IgE mediated, and it is therefore possible to get the incredible cascade of mediators leading to anaphylactic shock. It is also known that there are very potent substances found within the human body, which substances can cause release *in vivo* and *in vitro*. The present invention, in fact aims to detect potential allergens, which are found outside the human body. However, the present invention also has the potential of detecting and assessing mast cell activation by endogenous substances. It is known that a mammalian organism in response to external stimuli such as stress produces such substances. It is now known that endogenous cellular mediators, released by activated mast cells (e.g. mast cell proteases) or triggered eosinophils (e.g. rantes) induce mast cell degranulation and cause symptoms of allergy via a non-IgE-mediated mechanism. The present application represents the first instance that this was appreciated.

Benyon et al. in fact investigated substances, which caused release in the human body, and which correspond to the sort of substances, which applicant would be looking for, using the process of the invention.

Therefore, the Examiner is respectfully requested to reconsider and remove this rejection.

In paragraphs 7 and 8 of the Office Action, the Examiner rejects claims 44-53 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 35 and 46 have been cancelled. Therefore the rejection is moot as to these claims.

A. The Examiner asserts that in claim 44 the phrase "sensitizing agent" is unclear.

The Examiner's position is believed incorrect, as the specification is clear as to what constitutes a sensitizing agent. At page 3, lines 3-6, the specification states that allergen specific IgE molecules are also known as sensitizing agents. Further, at page 4, lines 1-4, the specification states that the sensitizing agent may comprise human serum or, alternatively, human IgE or a functional equivalent thereof.

Therefore, it is clear from the specification that the phrase sensitizing agent covers human serum, human IgE and functional equivalents thereof.

B. The Examiner alleges that in claim 47, the recitation of "high-secretor variant" is indefinite.

Claim 47 has been amended to delete reference to the degree of release. Therefore, the rejection is overcome.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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Date: December 16, 2002

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 45 and 46 are canceled.

The claims are amended as follows:

44. **(Amended)** A method for determining the allergenicity of a pre-selected substance comprising:

(a) exposing a mast cell-line and/or basophil cell-line to said substance in the absence of a sensitizing agent;

(b) detecting release of mast cell and/or basophil cell mediators in response to said exposing; and

(c) designating the pre-selected substance as potentially allergenic based on detecting release of mast cell and/or basophil cell mediators.

47. **(Amended)** A method according to claim 44, wherein said cell-line is a ~~high~~ secretor variant ~~which when exposed to a pre-selected substance results in at least 3-45% mediator release~~.

Claims 54 is added as a new claim.

54. **(New Claim)** A method according to Claim 44, wherein said cell line is an RBL-2H3 mast cell line which when exposed to a preselected substance results in at least 3-45% mediator release.